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THE VALUE OF AMORPHOUS CINCHONA
ALKALOID IN MALARIA



By E. E. WATERS, M.D., M.R.C.P. (London)

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Civil Surgeon, Hooghly



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DURING the malaria season of 1911 an investigation was commenced in the Medical College, Calcutta, as to the relative value of the Hydrochloride and Sulphate of Quinine in the treatment of malaria.

Some eighty cases were under observation and the conclusion arrived at was, that—taking the average of these cases—forty-five grains of either salt would in three days reduce the temperature to normal in any case of malarial fever, and that the Sulphate of Quinine was more effectual for this purpose than the Hydrochloride.

A few cases were treated with Cinchona Febrifuge, and as far as they went, it appeared that

this preparation was more effectual in malaria than either the Hydrochloride or Sulphate of Quinine.

This point seemed to deserve further investigation, and with the onset of the Malaria season of 1912 the matter was taken up again.

What is Cinchona Febrifuge? I cannot do better than quote from a letter of Sir D. Prain, issued by the Inspector-General of Jails, Bengal, in 1902.

"Cinchona Febrifuge differs from Quinine in two respects : (1) it is not a simple substance but a mixture of all the substances contained in Cinchona bark ; (2) it is not a crystalline but an amorphous product.

"The Febrifuge is a mixture of Quinine, Cinchonidine, Cinchonine, and Quinidine, which are present in varying proportions in Cinchona bark.

"The most important difference between the Febrifuge and either of the simple salts of Quinine or Cinchonidine is not that of chemical composition but of physical character. Besides the four alkaloids already enumerated, which are capable of being separated, every analysis of Cinchona bark shows a certain proportion of a fifth substance, which is termed *Amorphous Alkaloid*. There is reason to believe that this Amorphous Alkaloid is not a specific substance.

"All the Alkaloids of Cinchona are ordinarily presented to us as crystallizable salts, *i.e.*, Sulphate or Hydrochloride of Quinine, Cinchonidine, etc., but after the separation of these crystallizable salts other non-crystallizable substances remain, and it is these that are together known as Amorphous Alkaloid.

"It has been found that this amorphous substance, as an antiperiodic, is *much more effective than even pure crystallizable Quinine*, the reason being, apparently, that in this amorphous condition the alkaloid is *much more readily assimilated* by the system."

My attention was thus directed to the Amorphous Alkaloid rather than the Febrifuge, and, by the courtesy of Major Gage and Mr. G. E. Shaw,

the Government Quinologist, I was supplied with an ample stock of the drug and the following additional information :—

Mr. Shaw states—

“In the Cinchona bark there are quite a number of Alkaloids besides Quinine, which is, of course, the most valuable and which preponderates in all the Commercial barks. Many of these other alkaloids are crystalline and form crystalline salts by means of which they can be separated, but after this separation, a mixture still remains which is incapable of either crystallizing or forming any crystalline compound.

Our knowledge of Colloids has, so far, not advanced far enough to enable us to separate such a mixture into its constituents, though it is possible to make certain that there must be several there together. It is this mixture which has the name of Amorphous Alkaloid or Quinidine since Setherner discovered it in 1830.

“The amount in the bark varies greatly, from practically none to well over one per cent.

“We prepare it in the factory from the Quinine mother liquors by making successively insoluble salts of the remaining Quinine, the Cinchonidine and the Quinidine with their allied hydro bases, and then separating the Amorphous Alkaloid from the residue by its comparative insolubility in Solvents. Its price has been fixed at Rs. 4 per pound.”

So much for the composition and origin of the Amorphous Alkaloid. I will now discuss its action in malaria.

In the malaria season of 1912, a considerable number of cases of Malarial fever were admitted to the Imambarah Hospital, Hooghly, and, of these, 86 were treated with the Amorphous Alkaloid or with the Cinchona Febrifuge.

Twenty-seven cases were treated with two grains of Alkaloid thrice daily, 35 with four grains thrice daily, and 24 with five grains of Cinchona Febrifuge thrice daily. (*Vide* Table A.)

TABLE A.

Varieties of Malarial Fever treated with Amorphous Alkaloid and Cinchona Febrifuge.

	B. T.	M. T.	Quartan.	Total.	
Cinchona Alkaloid t.d.s.— 2-grains dose ...	11	13	3	27	One double infection. { B. T. Gamete form. M. T. Crescent form.
Cinchona Alkaloid t.d.s.— 4-grains dose ...	20	12	3	35	One double infection. { B. T. Gamete form. M. T. Crescent form.
Cinchona Febrifuge t.d.s.— 5-grains dose ...	9	14	1	24	One double infection. M. T. and sporulating quarters. One case M. T. Crescent & M. T. Ring form and many leucocytes.
Total treated ...	40	39	7	86	

In all cases the alkaloid was given in tablet form, as received from the Juvenile Jail, Alipore, the Febrifuge was given in freshly made pills. The doses were given with a drink of water, and in no special relation to meals—just as they happened to be due in the ordinary hospital routine.

No unpleasant effects of any moment were noticed from the Febrifuge—no nausea or ringing in the ears. A certain number of the patients taking the alkaloid—some eight or ten—complained of gastro-intestinal disturbance, such as diarrhoea, “heat in the stomach,” and so on, but this was far from common.

The patients selected for treatment were all suffering from malaria, that is to say, the particular parasite was detected and identified before treatment was commenced.

Further, in estimating the value of the drugs, it must be remembered that Hooghly is a particularly malarious district, where a little fever is lightly thought of, and that all the patients treated were sufficiently ill to give up their usual work and come into hospital for treatment.

TABLE B.

Average doses of Amorphous Alkaloid and Cinchona Febrifuge required to stop fever in Malaria.

	Average quantity of Amorphous Alkaloid to stop fever (per head).	Total average quantity of Amorphous Alkaloid given to each patient.
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I.—Amorphous Alkaloid, dose ii grs. t.d.s.

Benign Tertian cases	... 9 grains	22·5 grains.
Malignant Tertian cases	... 10·38 „	21 „
Quartan type cases	... 22 „	29·3 „

II.—Amorphous Alkaloid, dose iv grs. t.d.s.

Benign Tertian cases	... 13·8 grains	37·2 grains.
Malignant Tertian cases	... 16·6 „	46·8 „
Quartan type cases	... 24 „	48 „

III.—Cinchona Febrifuge dose v grs. t.d.s.

Benign Tertian cases	... 55 grains	78·3 grains.
Malignant Tertian cases	... 27·86 „	52·5 „
Quartan type cases	... 70 „	70 „

It is difficult in a mofussil hospital, with a limited staff, to determine when parasites are absent from the peripheral blood. Patients come to hospital suffering from fever and are anxious to leave when the fever has been stopped. The most practical method therefore of appraising the drug is to record how many grains are required to stop the fever which is the symptom from which the patient seeks relief.

The first series of 27 cases were treated with two grains of Amorphous Alkaloid thrice daily, with the following results. (Table B-I). Eleven benign tertian cases required an average of nine grains of alkaloid to stop fever.

Thirteen malignant tertian cases required ten and half grains of alkaloid to stop fever.

Three quartan cases required twenty-two grains to stop fever.

Fuller details of these patients, with illustrative charts, of the severer cases are appended—

TABLE C.

Sew Dut Tewari (Chart I) had suffered from fever for 4 or 5 days before admission to hospital. Parasites (B. T.) were present in his blood. Eighteen grains of Amorphous Alkaloid brought the temperature to normal.

Nister, female (Chart II), had fever for 8 days before admission to hospital. Parasites B. T. gametes were in the blood. Temperature rose to 105°. Six grains of Amorphous Alkaloid stopped the fever. No relapse whilst in hospital.

G. H. Blake, European (Chart III), admitted with history of 5 days fever. Had vomiting and gastric catarrh. Liver much enlarged, tongue dry. Very ill. Had tramped about the country in search of work. M. T. parasite discovered on 4th day after admission. Six grains of Amorphous Alkaloid stopped the fever. No relapse whilst in hospital.

Topi Ram (Chart IV) had repeated attacks of fever for 21 days, and continuous fever for 11 days before admission. Spleen not enlarged. Low muttering delirium. Diarrhœa.

Gobindo Doyal (Chart V). Repeated attacks of fever before admission. Spleen enlarged. Quartan parasite in the blood. Twelve grains of Alkaloid reduced the temperature to normal. No relapse whilst in hospital. This patient suffered from "dysentery" after the fever and ascribed it to the medicine.

Having procured a series of cases with two grains of Amorphous Alkaloid thrice daily, I decided to try the effect of a larger dose, particularly as it appeared in one or two cases that the two-grain dose was not quite enough to control the fever.

To the second series of 35 cases, the Amorphous Alkaloid was given in four-grain doses, generally thrice daily, but in a few cases twice daily only. In this series there were 20 benign tertian, 12 malignant tertian, and 3 quartan.

The results were as follows :—

20 benign tertian cases required $13\frac{1}{2}$ grains to bring the temperature to normal.

12 malignant tertian cases required $16\frac{1}{2}$ grains.

3 quartan cases required 24 grains.

It thus appears at first sight that the larger doses were less effective than the small ones, but this, I think, is not really the case. The difference is not large and is probably accounted for by the drug being given in larger quantities in each day and so over-running the fever to some extent. The benign tertians required less alkaloid than the malignant, whilst the quartans, true to their reputation, required considerably more than either.

The following cases, with Charts, are examples:—

Ram Golush Roy had been suffering from continuous fever for 3 or 4 days. On admission collapsed with severe purging and vomiting. Pulse irregular and intermittent, much prostration. An excellent example of the pernicious or Algid type of malaria. This is the most interesting case of the series. The patient was dangerously ill on admission and apparently suffering from cholera, but the M. T. rings were found in the blood. On the day of admission the temperature was subnormal and the condition desperate; on the second day the temperature was still subnormal and the man very ill; on the third day Amorphous Alkaloid, grains xii, were given. There was an attack of fever in the evening, and though the man was very ill, he was not quite so ill as on the first day. The temperature rose only to 99°. The next day there was no attack; the man was fairly well and the alkaloid was continued. On the 5th, there was a sharp attack of fever in the afternoon, the temperature reaching 103°, but the patient said he felt much better, and his general appearance confirmed this. There was no prostration nor any of the typical pernicious signs, and *after this the patient had no further attacks*. It seems, therefore, that the improvement in the man's condition was definitely indicated by the rise of his temperature—a sign which is new to me and which I have not seen in the books.

Vide Chart VI.

Kushem—(23). The patient had been suffering from fever for 10 days before admission. The spleen was enlarged. Malignant tertian parasites found. Cinchona Alkaloid, grains iv t.d.s. were given and rapidly reduced the temperature to normal.

Vide Chart VII.

(10) *Sukhur Gwala*—Admitted on 17-9-'12. Had suffered from repeated attacks of fever for 3 weeks. His spleen was enlarged. Young benign tertian parasites in the blood. Alkaloid, grains iv, thrice daily—24 grains in all, aborted the next attack. Patient discharged cured on 22nd.

Vide Chart VIII.

(9) *Kali Kristo Banerji*—Admitted on 2-10-'12. Had suffered from repeated attacks of fever for four months,

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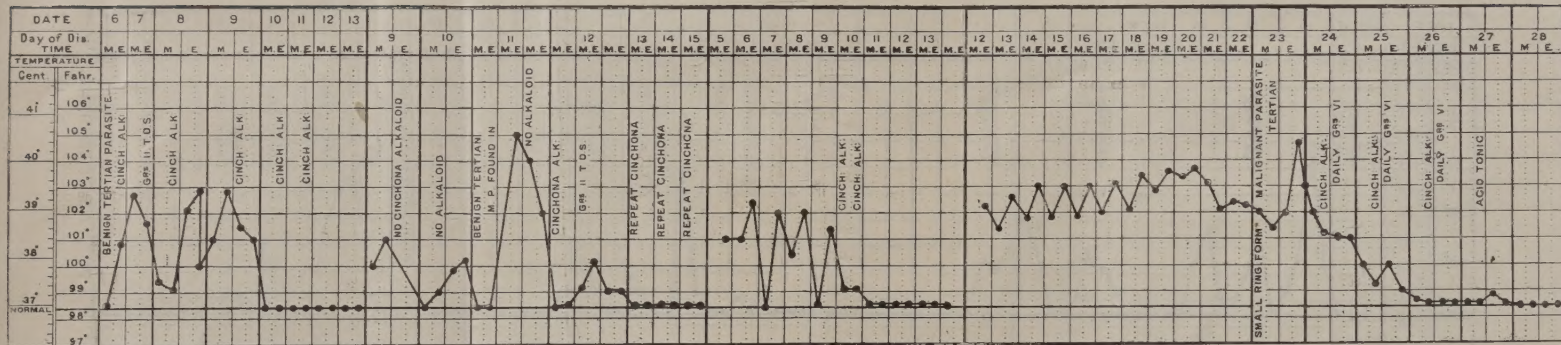
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I

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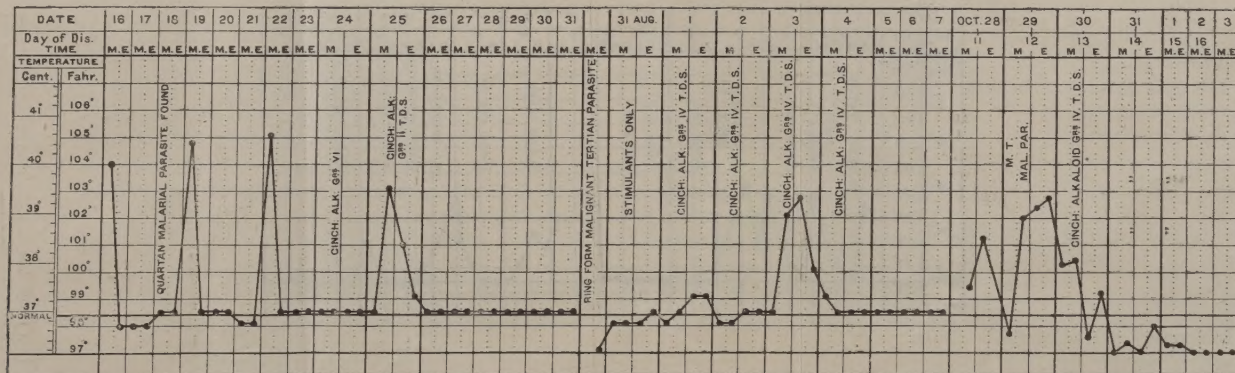
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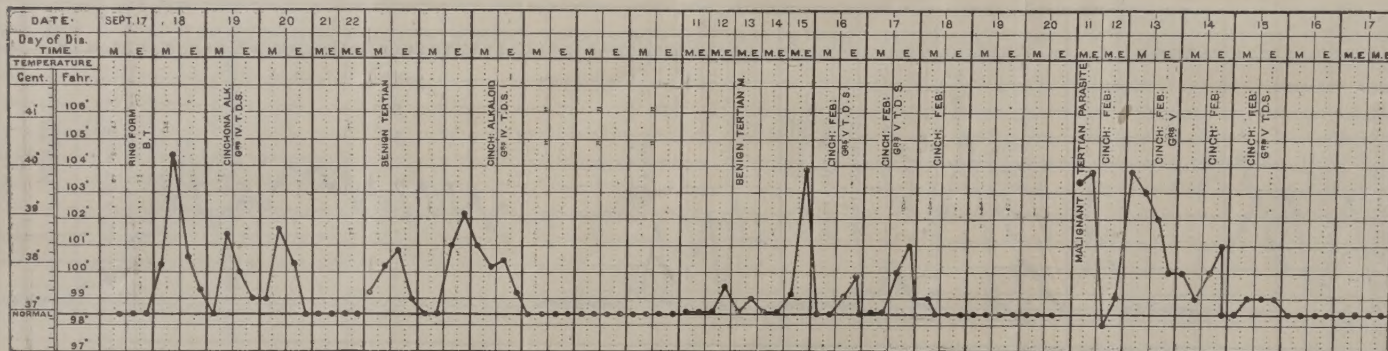
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IX

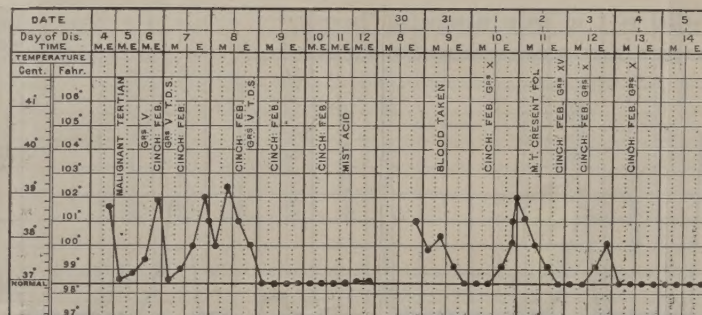
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XI



XII

XIII



each attack lasting for eight or nine days. Spleen not enlarged, jaundice. Young benign tertian parasites in the blood. Alkaloid, grains iv, thrice daily. Twelve grains stopped the fever. No relapse whilst in hospital.

Vide Chart IX.

The above are the typical cases treated with the four-grain doses of the Cinchona Alkaloid.

CINCHONA FEBRIFUGE.

Having obtained a series of cases treated with the Amorphous Alkaloid, I reverted to the use of Cinchona Febrifuge.

It will be seen that this drug must be used in considerably larger dose than the Amorphous Alkaloid in order to produce the same effects. This is to be expected from the relative composition of the two substances. I am disappointed that the results of the 1912 cases are not as good as those of 1911, but one or two very resistant cases considerably raised the average amount of febrifuge required.

The following cases are representative ones.

Hari Das had suffered from fever for one month before admission, and continuously for 10 days. Spleen enlarged. Benign tertian parasite. Forty grains of Febrifuge stopped the fever.

Vide Chart X.

Asutosh Sil.—History of 8 days fever before admission with vomiting. First seen on ninth day. Malignant tertian parasite. Spleen enlarged. Sixty grains of Febrifuge stopped the fever.

Vide Chart XI.

Gonopati Benia had fever continuously for 3 days before admission. Spleen not palpable. Malignant tertian parasite. Thirty grains of Febrifuge stopped the fever.

Vide Chart XII.

Jagai Dharka.—Table E (14). First seen on 8th day. Complained of fever for one week before admission. Crescents in the blood. Spleen enlarged. Some bronchitis. Forty grains of Febrifuge stopped the fever.

Vide Chart XIII.

The cases detailed above—of which the Charts are abbreviated for reasons of space—may fairly be taken to prove that the Amorphous Alkaloid (and the Cinchona Febrifuge) are efficient remedies for malaria. I have demonstrated that excluding quartan cases, *an average of sixteen grains of this Alkaloid is sufficient*—taking every case in a series of 62—to stop the fever in malaria, and to stop it very promptly after it has been persisting for some days.

In other words, *the Amorphous Alkaloid is from three to five times as effectual as quinine sulphate, and may therefore be given in proportionately smaller doses.*

It has no unpleasant effects, can be given in small tablets, is rapidly effectual, *and is inexpensive.*

This last point is perhaps one of the most important, certainly from the administrative point of view. It is rumoured that a powerful combine controls most of the quinine supplies of the world and that prices are rising. Quinine Hydrochloride is about Rs. 16 per pound, the Sulphate about Rs. 8/8 to Rs. 10 per pound, and it is the Hydrochloride that has been asked for in some provinces for distribution in “treatments.” Now, a pound of Hydrochloride, at sixteen rupees, will make 1,400 five-grain tablets, whilst a pound of Amorphous Alkaloid, at four rupees, will give 3,500 two-grain tablets of equal

efficacy. In other words, four rupees worth of Amorphous Alkaloid, now almost a waste product, will do the work of forty rupees worth of Quinine Hydrochloride.

For this reason alone, the Alkaloid is worthy of a more extended trial, and I commend its use to Civil Surgeons and others in whose annual budgets expenditure for quinine is an unpleasantly heavy item.

My thanks are due to Assistant-Surgeon Kali Mohan Sen and the staff of the Imambarah Hospital for their assistance in collecting the material for this paper.

WE direct the attention of all interested in the quinine question and in the treatment of malarial fevers to the paper we publish in this issue by Major E. E. Waters, M.B., M.R.C.P., I.M.S., the Civil Surgeon of Hooghly.

*Editorial
note*

The amorphous cinchona alkaloids have been hitherto considered more or less as a waste or bye-product of quinine manufacture, but their value has been for some time appreciated by missionary medical men in India.

The supply of quinine available in the world is at present limited and likely to be so for some time, as except for the plantations possessed by the Government of India the world's supply is controlled by a body of merchants in Hamburgh, and the more that anti-malarial operations are taken up in tropical countries, the more will the demand for quinine increase and its price must necessarily rise.

From this it follows that it has become vitally necessary to make the most use of the cinchona now possessed by the Government of India.

Major Waters shows that these amorphous alkaloids are of real value in malarial fevers, that the dose required is small and that the drug is cheap. If therefore these amorphous alkaloids can largely replace quinine, the saving of public money will be great.

We therefore call the attention of our readers to these facts, and we may inform them that amorphous cinchona alkaloid is now obtainable either in powder or in tablet form (2 grain, $3\frac{1}{3}$ grain or 4 grain tablets) from the Superintendent, the Juvenile Jail, Alipore, Calcutta, at a price just over Rs. 4 per lb. We may add that the Superintendent of the Juvenile Jail in the year 1912 supplied no less than 512 lbs. of the amorphous alkaloids chiefly to Mission Hospitals, and is ready to supply demands for the present year.

[For reasons of space we have omitted a long table giving details in tabular form of the whole series of cases. That Major Waters has proved his case as to the value of the Amorphous Alkaloid is sufficiently clear from the cases quoted above.—ED., *I. M. G.*]



